

Newer Therapy for Leukemia, Polycythemia, and Lymphoma

ARTHUR A. MARLOW, M.D., and GRANT R. BARTLETT, Ph.D., La Jolla

X-RADIATION was the only specific treatment for leukemia and lymphoma until recently. It is the treatment of choice in many instances. However, alternate therapy for these and other allied conditions is now available.

Chronic leukemia

A great deal can be accomplished in the treatment of chronic leukemia if it is borne in mind that present treatment is palliative. The whole patient, rather than the diagnosis or the leukocyte content of the blood, should be treated. Osgood⁵ recommended the treatment of chronic leukemia from the date of discovery, regardless of symptoms. He maintained that patients can be kept in happier and more productive states during their remaining years by this method. He emphasized follow-up at intervals regularly spaced to determine the effects of radiation before further treatment is applied. Block and Jacobson¹ expressed the opinion that specific therapy should be reserved for patients with symptoms of active disease — an opinion concurred in by the majority of investigators. Ross and Ebaugh⁸ noted that available specific agents destroy normal as well as neoplastic cells and suggested that they be used with care.

The advisability of a conservative attitude toward specific therapy is illustrated by the cases of two patients under the authors' observation. One, an unmarried white woman, a teacher, was referred to the authors 11 years ago in 1941, at the age of 56. Chronic lymphatic leukemia had been discovered five years before, in 1936. As the patient remained in good health, specific treatment had not yet been started at the present writing. The other, who is being treated, is a white man 74 years of age with a well documented diagnosis of chronic lymphatic leukemia made 29 years ago in 1923.

X-radiation is the preferred treatment at present. Radioactive phosphorus is used with increasing frequency because of the absence of radiation sickness and the ease of administration. It may become the treatment of choice as experience with it increases.

• X-radiation remains the treatment of choice in most cases of leukemia and lymphoma, but new agents are playing an increasing role in therapy. Radioactive phosphorus does not produce radiation sickness and results with it are comparable to those of x-ray therapy in chronic leukemia. Urethane and nitrogen mustard may produce remissions in patients with chronic leukemia who have become resistant to radiation. Triethylene melamine may be administered orally with nitrogen mustard-like effects and is undergoing further trial. Aminopterin, ACTH and cortisone often cause short remissions in acute leukemia. Urethane is the best treatment available for multiple myeloma. Polycythemia vera is well controlled by radioactive phosphorus combined with venesection. Nitrogen mustard is often effective and triethylene melamine shows promise in Hodgkin's disease. Anti-anemic substances such as iron and liver extract are of no value in the treatment of anemia caused by leukemia, lymphoma and myeloma.

Urethane⁶ produces clinical results comparable to those of radiation in a majority of patients with chronic myelogenous leukemia. Results are somewhat less satisfactory in chronic lymphatic leukemia. The enteric coated tablets are well tolerated by most patients in average doses of 1 gm. three times daily after meals. Often the dose can be reduced to 1 or 2 gm. daily for maintenance. Therapy must be continuous or relapse will occur quickly. The authors feel (without statistical proof) that patients cannot be maintained as long with urethane as with radiation and therefore reserve urethane for trial chiefly in chronic myelogenous leukemia which has become refractory to radiation. Chart 1 illustrates the prolongation of life by approximately one year in chronic myelogenous leukemia by use of urethane after x-radiation became ineffective.

Nitrogen mustard has produced very satisfactory remissions and it may be used as alternative therapy in patients who no longer respond to radiation. Nausea and vomiting have restricted its use but the authors have had surprisingly little trouble with this

From the Scripps Metabolic Clinic, La Jolla.

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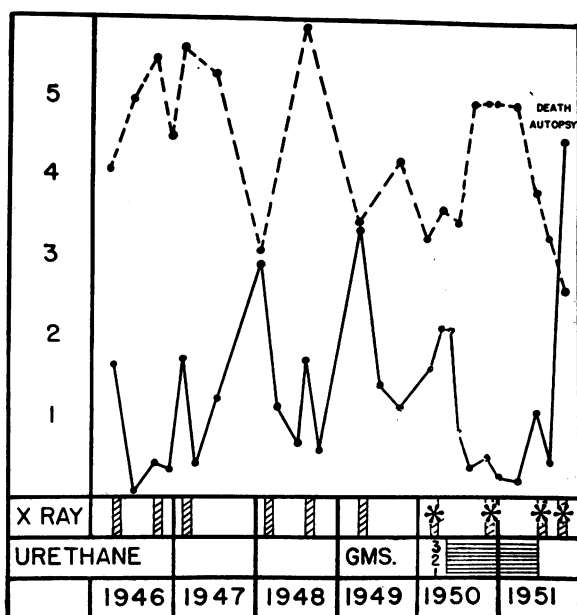


Chart 1.—Effect of urethane after patient no longer responded to x-radiation in a case of chronic myelogenous leukemia. The interrupted line indicates erythrocytes in millions per cu. mm. of blood, and the continuous line leukocytes in hundred thousands per cu. mm. X-ray therapy without response is indicated by asterisks. The patient was a man 26 years of age.

complication when 0.2 gm. of Amytal Sodium® are given by mouth at the end of the intravenous infusion.

Triethylene melamine (TEM),⁹ a 5 mg. tablet with nitrogen mustard-like effects, can be given by mouth with little difficulty from nausea and vomiting. It offers considerable promise as a convenient method of treatment. However, it is a powerful bone marrow depressant and more experience will be necessary before it can be released for general use.

Monocytic leukemia often runs a subacute course and is resistant to therapy, although more chronic types may respond to x-radiation.

The authors have had poor results in general with the treatment of chronic leukemia in patients who have leukopenia at the outset. However, therapy should always be attempted as some patients will respond satisfactorily to radiation.

Acute Leukemia

The treatment of acute leukemia, regardless of cell types, remains unsatisfactory. (Although the authors are inclined at times to recommend no treatment, this is a recommendation that patients' relatives will not accept.) Now there are two specific agents which influence the disease, although results are often disappointing.

Aminopterin* and other folic acid antagonists can be given conveniently by mouth and they will

* Supplied through the courtesy of Lederle Laboratories, Division of the American Cyanamid Co., New York, N.Y.

produce remissions, often of several months' duration, in 25 to 50 per cent of children. Such remissions are uncommon in adults. Toxic manifestations such as stomatitis, diarrhea, skin and mucous membrane hemorrhage, pancytopenia and alopecia may be troublesome or disastrous.¹⁰ Aminopterin is given in average doses of 0.5 mg. daily until improvement is noted or toxic symptoms appear. Either effect is usually apparent within two weeks. It is customary to stop the drug when improvement occurs, as there is little evidence that maintenance therapy prolongs remission. Therapy may be reinstituted when signs of relapse occur, but the results of subsequent courses of treatment are often less satisfactory.

Hormone therapy with corticotropin (ACTH) or cortisone produces a gratifying sense of well-being, and remissions are obtained in about 50 per cent of patients. The remissions are often short and may last only a few days or a few weeks. Restriction of the dietary intake of sodium chloride to 1 gm. or less per 24 hours is necessary to prevent troublesome edema. Supplementary therapy with enteric coated tablets of potassium chloride, 3 to 8 gm. daily, will offset increased potassium loss owing to use of these hormones. Results of the alternate use of hormones and folic acid antagonists have been reported recently.⁷

Multiple Myeloma

Multiple myeloma is one of the most malignant and painful tumors of the blood-forming organs. An occasional case with a more benign course is seen, but management of patients with this disease has always been difficult. X-radiation has afforded some relief in the past but urethane is the best treatment available at this time.⁴ Urethane is not effective in all instances and gastrointestinal intolerance prevents its use in some patients. Three or 4 gm. are given daily for treatment, and maintenance doses of 1 to 3 gm. daily may be given for long periods. Leukopenia occurs frequently when the drug is given on that schedule, but it is tolerated well. Favorable response—general improvement and relief of bone pain and anemia—usually begins within two or three weeks. Recalcification of bone lesions may occur during urethane therapy (Figure 1). The authors employed prefrontal lobotomy with success for the relief of intractable bone pain in one case of myeloma. In the management of a patient treated recently, corticotropin and cortisone were useful for the control of pain while waiting for urethane effects.

Polycythemia Vera

Radioactive phosphorus, given in small doses of about 3 millicuries by mouth, appears to be the simplest and most effective treatment for polycythe-

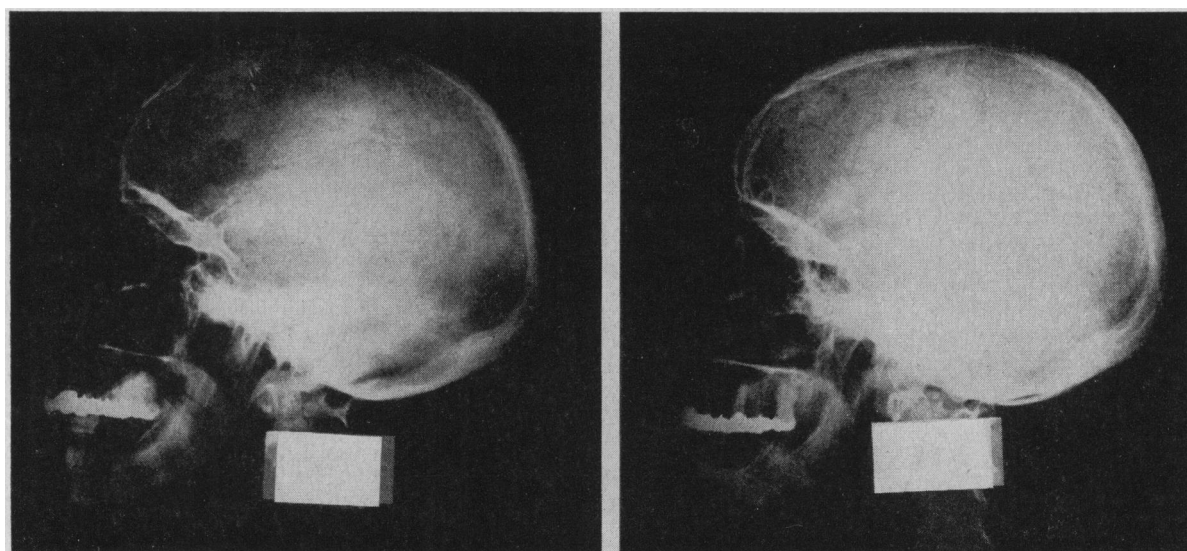


Figure 1.—Recalcification during urethane therapy for multiple myeloma in a white woman 63 years of age.

Choice of Therapy in Leukemia, Polycythemia, and Lymphoma

	X-Ray	P ₃₂	Urethane	HN ₂	Cort. ACTH	Aminopterin
Chronic leukemia, myelogenous.....	1	1	2	3
Chronic leukemia, lymphatic.....	1	1	3	2
Acute leukemia, all types.....	1	1
Multiple myeloma	2	..	1
Polycythemia vera	1†
Lymphosarcoma	1	3	..	2
Giant follicular lymphoma.....	1	3	..	2
Hodgkin's disease	1	2

Key: 1 = first choice; 2 = second choice; 3 = third choice.

†Combined with venesection.

mia. As effects do not become apparent for 30 to 60 days, preliminary venesection to reduce the blood cell volume to about 55 per cent of the whole blood is done for immediate relief of symptoms. Patients may be retreated at intervals of three months with 2 or 3 millicuries of radioactive phosphorus and venesection may be repeated if necessary. Remissions for two years or more have been produced by this method.³ The authors had excellent results during a short follow-up period up to two years in ten of eleven cases.

Lymphosarcoma, Giant Follicular Lymphoma and Hodgkin's Disease

Radical surgical removal of solitary tumors with the hope of an occasional cure has been revived recently.² The operation should be followed by heavy local radiation. This method had not been looked upon with favor, as recurrence at other sites usually took place. The subject is a controversial one, but enough "cures" of five years or more have been reported to recommend serious consideration for an occasional carefully selected case.

X-radiation is the treatment of choice for lesions of the lymphoma group. Results with radioactive

phosphorus have been disappointing in most hands, although Block and Jacobson¹ considered it as effective as x-ray in lymphosarcoma and giant follicular lymphoma.

Nitrogen mustard deserves an important place in the treatment of Hodgkin's disease, especially if the patient has severe toxic symptoms and widespread disease. It is useful for the rapid relief of symptoms of acute pressure, especially in the case of mediastinal obstruction where x-ray therapy may be dangerous. Nitrogen mustard is generally less effective in lymphosarcoma and giant follicular lymphoma than in Hodgkin's disease. However, it deserves a place as alternate trial therapy in these conditions. Melamine has shown considerable promise as a convenient palliative agent in the treatment of Hodgkin's disease. Corticotropin and cortisone have been of little assistance, but the authors have seen an excellent result of six months' duration in one case of Hodgkin's disease which had become resistant to x-ray.

The anemia caused by leukemia, lymphoma and myeloma responds only to specific therapy and transfusions. Antianemic substances such as iron and liver extract are of no value.

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A.M.E.F. Funds Total More Than \$886,430

CONTRIBUTIONS to the American Medical Education Foundation in 1952 totaled more than \$886,430. This includes an American Medical Association grant of \$500,000 voted by the House of Delegates in December 1951 at Los Angeles. In all, 6,739 contributions have been recorded from 6,697 individuals, 11 laymen and 31 organizations.

Distribution of Class A grants for the 79 medical schools in the country was made in August—\$15,000 for each of the 72 four-year schools; \$7,500 for each of the six two-year schools, and \$11,250 for one three-year school.

Particularly encouraging . . . contributors up 4,863 over 1951 . . . total receipts up \$140,513 over 1951.—From *A.M.A. News Notes*.